The Rejection of Claims 25-26 under 35 USC 112, ¶1

Claims 25-26 were rejected under 35 USC 112, ¶1, with the Examiner contending that the specification, while enabling for CMV, does not reasonably provide enablement for treating herpes viruses generally.

This rejection, as applied to amended Claims 25 and 26, is respectfully traversed.

Claim 25 has been amended to recite that the infection is an infection with a virus selected from herpes simplex virus and cytomegalovirus. The Examiner has agreed that enablement for the treatment of infection with cytomegalovirus has been shown. Enablement for the treatment of infection with herpes simplex virus is provided by the statements in the specification, e.g. at page 13, lines 13-27 previously referred to. Further enablement is provided by the statements in the specification at page 1, lines 40-42, showing that ganciclovir is effective for the treatment of herpes simplex viral infections (referring to US Patent No. 4,355,032). Because ganciclovir mono(L-valinate), and hence crystalline GMVH, is a prodrug of ganciclovir, it will necessarily have the same general activity as ganciclovir, so the use for the treatment of herpes simplex viral infections is established.

Withdrawal of the rejection is requested in view of the amendment.

The Rejection of Claims 23-28 under 35 USC 102(b) over Beauchamp

Claims 23-28 were rejected under 35 USC 102(b) as being anticipated by Beauchamp, US Patent No. 5,043,339 (**Beauchamp**).

This rejection, as applied to amended Claims 23-28, is respectfully traversed.

The Examiner's rejection of Claims 23-28 under 35 USC 102(b) as being anticipated by **Beauchamp** is based on two premises: first, that the genus of compounds disclosed by **Beauchamp** is sufficiently small that each member of the genus is considered anticipated (i.e. so that the compound GMVH is considered anticipated), and second, that the

limitation in Claims 23-28 to *crystalline* GMVH is of no patentable significance, so that if the compound GMVH is in any way disclosed by **Beauchamp**, then crystalline GMVH is also anticipated.

(1) The Examiner contends that the compound GMVH is anticipated by the disclosure of **Beauchamp**, because the genus of compounds disclosed is sufficiently small that each member of the genus is considered disclosed (a Petering-type anticipation, after *In re Petering and Fall*, 133 USPQ 275 (CCPA 1962)). Applicants respectfully disagree.

Beauchamp discloses mono- and bis-amino acid esters of ganciclovir and its cytosine analog, with a preference for aliphatic amino acids containing up to six carbon atoms (such as glycine, alanine, valine, and isoleucine), in either the D-, L-, or D,L- form, preferably the L- form, and that these compounds may be prepared as pharmaceutically acceptable acid addition salts, listing nine acids, including hydrochloric acid, as being suitable. It is undisputed that **Beauchamp** discloses the preparation of four ganciclovir bis(amino acid esters) and two esters of the cytosine analog, all as the acetate salts, including ganciclovir bis(L-valinate) as the acetate salt; and that **Beauchamp**'s preparation of ganciclovir bis(L-alaninate) resulted in a mixture of ganciclovir mono(L-alaninate) and ganciclovir bis(L-alaninate) in a 1:9 ratio as a syrup.

Applicants respectfully submit the teaching of **Beauchamp** is not so specific, particularly when considering that all of the examples describe the synthesis of bis(amino acid esters) and the only disclosure of a mono(amino acid ester) is as a 10% impurity in the preparation of a bis(amino acid ester), as to constitute an enabling disclosure of the synthesis of ganciclovir mono(L-valinate) hydrochloride. Applicants therefore submit that, even under the standards of *In re Petering and Fall*, ganciclovir mono(L-valinate) hydrochloride is not anticipated by **Beauchamp**.

(2) Even if it were assumed, *arguendo*, that the compound GMVH is known, that does not imply that crystalline GMVH is also known, nor that the limitation to crystalline GMVH may be ignored in determining the patentability of the claims.

It is settled law that, to anticipate a claim, a reference must show every element of the claim. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal*

Bros. v. Union Oil Co. of California, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987); "The identical invention must be shown in as complete detail as is contained in the ... claim." *Richardson v. Suzuki Motor Co.*, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989), both quoted at MPEP 2131.

Thus, even if the compound GMVH were considered anticipated by the disclosure of **Beauchamp**, **Beauchamp**'s disclosure does not include *crystalline* GMVH, since **Beauchamp** shows no compounds in crystalline form.

In response to this argument, the Examiner has contended that "art rejections cannot be avoided simply by describing the compound in greater detail than the prior art, and that is exactly what the 'crystalline form' argument does." He then analogized by referring to possible claim limitations to a particular melting point, refractive index, or specific gravity, and asserted that such descriptions merely describe the same compound more fully and are of no patentable significance. Applicants respectfully disagree, as the Examiner's assertion begs the real question, which is "*do* the limitations merely describe the same compound more fully?". *If* the limitations in fact merely describe the same compound more fully, then it could be said that a claim with the additional limitations is inherently anticipated by the disclosure of the same thing without the limitations; but the Examiner has pointed to nothing in **Beauchamp** that would suggest that crystallinity is an inherent property of GMVH, i.e. that no matter how GMVH were prepared it would *always* (the basic requirement for inherency) be crystalline. In fact, not only did **Beauchamp** not prepare GMVH at all, let alone in crystalline form, none of the compounds prepared by **Beauchamp** were stated to have been prepared in crystalline form, so there is no suggestion in **Beauchamp** of the inherent crystallinity of such compounds.

Applicants are clearly capable of preparing crystalline GMVH, as its preparation is described in the application itself. However, Applicants are equally capable of preparing GMVH in non-crystalline form: GMVH does not inherently (i.e. regardless of the method of preparation) appear in crystalline form, although Applicants have been able to cause it to crystallize.

What, then, is a fair test of the "inherency" of crystallinity of GMVH, when **Beauchamp** does not disclose the compound itself and equally does not disclose any hydrochloride salt? Applicants submit that if a person of ordinary skill in the art, reading **Beauchamp**, would find that the closest analogous compound prepared by **Beauchamp** were non-

crystalline, such a person would not consider GMVH to be inherently crystalline, so that the limitation in the claims to *crystalline* GMVH in fact constitutes the disclosure of a novel and unobvious material.

Applicants submit that the closest compound in **Beauchamp** is ganciclovir bis(L-valinate) acetate, the compound of **Beauchamp**'s Example 5. Applicants have therefore undertaken extensive studies in an attempt to prepare ganciclovir bis(L-valinate) acetate in crystalline form, and enclose herewith the Declaration of Dr. Hans Maag describing some of the attempts and results [further attempts by Mr. Charles Dvorak, not described in Mr. Dvorak's Declaration, were equally unsuccessful]. As seen in the Declaration, numerous attempts by Dr. Maag [a person of more than ordinary skill in the art, since he is both an inventor of the subject matter of the present application and also a scientist who has spent considerable time working with ganciclovir esters] to prepare ganciclovir bis(L-valinate) acetate in crystalline form have been unsuccessful; and both he and Mr. Dvorak opine that it will not be possible to prepare ganciclovir bis(L-valinate) acetate in crystalline form.

A person of ordinary skill in the art, considering **Beauchamp**'s disclosure of six non-crystalline esters (three "foams", one "white solid", one "syrup, turning solid on scraping" [this being ganciclovir bis(L-valinate) acetate], and one "syrup") and this information, would conclude that ganciclovir bis(amino acid esters) and particularly ganciclovir bis(L-valinate) would not be crystalline. Therefore, it could not be expected that a ganciclovir mono(L-valinate) derivative would be capable of crystallization, far less inherently crystalline.

As a further demonstration, and bearing in mind that the compound of the present invention is crystalline ganciclovir mono(L-valinate) hydrochloride, Applicants have therefore undertaken further extensive studies in an attempt to prepare ganciclovir bis(L-valinate) hydrochloride in crystalline form. Enclosed herewith are the Declarations of Mr. Charles Dvorak and Dr. Yeun-Kwei Han, describing the attempts and results. As seen in the Declaration, numerous attempts by Mr. Dvorak and Dr. Han [both persons of more than ordinary skill in the art, since both are scientists who have spent considerable time working with ganciclovir esters] to prepare ganciclovir bis(L-valinate) hydrochloride in crystalline form have been unsuccessful; and both opine that it will not be possible to prepare ganciclovir bis(L-valinate) hydrochloride in crystalline form without undue effort, if at all.

With regard to the Examiner's specific comments on the appropriateness of the Petering-type rejection in view of the lack of disclosure in the reference, Applicants respectfully submit that there is a difference between them in how much a Petering-type reference need show in order to be anticipatory when there is a doubt as to inherency. With due respect, this is not a case where GMVH has been disclosed in crystalline form and Applicants are claiming a particular morphology, this is a case where GMVH is *deemed to be disclosed* only by virtue of being a member of a genus that is disclosed; no disclosed member of the genus has been disclosed to be crystalline; and Applicants have shown that the closest disclosed member of the genus (and even a yet closer analog not disclosed) are non-crystalline.

Accordingly, Applicants submit that **Beauchamp** does not anticipate crystalline GMVH, and that the rejection of Claims 23-28 as amended [to crystalline GMVH, to antiviral pharmaceutical compositions containing it, and to methods for its use in the treatment of infections with herpes simplex virus and cytomegalovirus, i.e. every claim requiring crystalline GMVH] under 35 USC 102(b) over **Beauchamp** should therefore be withdrawn.

Withdrawal of the rejection is requested.

The Rejection of Claims 23-28 under 35 USC 103(a) over Beauchamp

Claims 23-28 were rejected under 35 USC 103(a) as being unpatentable over Beauchamp, US Patent No. 5,043,339 (**Beauchamp**).

This rejection, as applied to amended Claims 23-28, is respectfully traversed.

First, Applicants submit that crystalline GMVH is not anticipated by **Beauchamp**, as discussed above.

Second, Applicants submit that **Beauchamp** not only does not anticipate crystalline GMVH, it does not suggest it.

Applicants incorporate here by reference the arguments made above with respect to the non-anticipatory status of **Beauchamp**, as these same arguments also go directly to the non-obviousness of crystalline GMVH. The Examiner's argument with respect to crystallinity appears to be that since it is a desirable property (as stated by Applicants), it would be expected that one of ordinary skill in the art could produce crystalline GMVH if desired, so that it is incumbent on

Applicants to show the unexpected nature of crystalline GMVH. Applicants respectfully disagree, as they believe that this misapplies the burden of proof. The Examiner has pointed to no language in **Beauchamp** indicating possession of any crystalline compound in those made or disclosed, no statement in the specification indicating knowledge of the crystallinity of the compounds of the patent, and no motivation for even the attempt to prepare a crystalline compound (let alone crystalline GMVH). When the only mono-ester [ganciclovir mono(L-alaninate)] exemplified in **Beauchamp** is present as an incidental impurity in the corresponding bis-ester, and when the identical synthetic method applied to the L-valinate ester produces only the bis(L-valinate) without disclosed crystallinity, Applicants respectfully submit that it is incumbent on the Examiner to do more than simply assert that crystalline GMVH is obvious because it would be desirable. And, the Examiner's statements to the contrary notwithstanding, **Beauchamp** does not teach crystalline GMVH.

Furthermore, as shown above, Applicants have demonstrated that the closest disclosed compound, ganciclovir bis(L-valinate) acetate, is non-crystalline and, in the opinion of persons of at least ordinary skill in the art, is incapable of being prepared in crystalline form; and even that a non-disclosed closer analog, ganciclovir bis(L-valinate) hydrochloride, is non-crystalline.

Accordingly, Applicants submit that **Beauchamp** neither discloses nor suggests crystalline GMVH, and the rejection of Claims 23-28 as amended [to crystalline GMVH, to antiviral pharmaceutical compositions containing it, and to methods for its use in the treatment of infections with herpes simplex virus and cytomegalovirus, i.e. every claim requiring crystalline GMVH] under 35 USC 103(a) over **Beauchamp** should therefore be withdrawn.

Withdrawal of the rejection is requested.

The Rejection of Claims 23-28 under 35 USC 103(a) over Verheyden et al. in view of Beauchamp et al.

Claims 23-28 were rejected under 35 USC 103(a) as being unpatentable over Verheyden et al., US Patent No. 4,355,032 (**Verheyden et al.**) in view of Beauchamp et al., *Antiviral Chemistry and Chemotherapy*, **3**(3), 157-164 (1992) (**Beauchamp et al.**)

This rejection, as applied to amended Claims 23-28, is respectfully traversed.

Claims 23-28 were rejected as obvious over **Verheyden et al.** in view of **Beauchamp et al.**, with the Examiner reasoning that since **Verheyden et al.** shows ganciclovir, and **Beauchamp et al.** shows that acyclovir valinate is substantially more bioavailable than acyclovir, and since ganciclovir and acyclovir are similar "one skilled in the art would find it reasonable to infer information from one about the other", then it would be obvious to prepare GMV. With regard to the elements of the hydrochloride salt and crystallinity, the Examiner says, in effect, that the hydrochloride salt is suggested by **Beauchamp et al.**'s acyclovir hydrochloride, and that crystallinity is suggested by the recrystallization described in **Beauchamp et al.**'s Method A. Applicants respectfully disagree.

Verheyden et al. shows only ganciclovir and its pharmaceutically acceptable salts (of which the broad disclosure includes both acid addition salts and salts formed with bases, but the only compound exemplified is the sodium salt). There is neither disclosure nor suggestion in **Verheyden et al.** of any esters of ganciclovir. **Beauchamp et al.** shows a number of amino acid esters of acyclovir, including the L-valinate ester and its hydrochloride salt. Acyclovir L-valinate (valacyclovir) hydrochloride is said to be the best of these esters as prodrugs for acyclovir.

First, the Examiner reasons that it would be obvious to prepare GMV based on the attractiveness of acyclovir mono(L-valinate). Appellants cannot agree. While acyclovir valinate is a suitable prodrug of acyclovir, this does not lead to the conclusion that GMV is a suitable prodrug of ganciclovir. Esterification of ganciclovir, without some specific procedure involving blocking of one of the two hydroxy groups or a method of selective de-esterification, will tend to produce the bis-ester or at best a mixture of the mono- and bis-esters, which is not the crystalline GMVH of the claims. Never mind, says the Examiner, the combination of references suggests both the mono- and bis-esters, because **Beauchamp et al.** is a mono-ester, and one of ordinary skill in the art would know how to produce a mono-ester if desired. However, acyclovir L-valinate is a mono-ester because there is only one hydroxy group to esterify, unlike ganciclovir, which has two. What is more, to say that one of ordinary skill in the art would know how to produce a mono-ester if one were

desired does not establish that one would want to produce a mono-ester, that is, the Examiner has failed to establish within the references the motivation for the preparation of GMVH. Appellants submit that a fair reading of **Verheyden et al.** in view of **Beauchamp et al.** would suggest only bis-esterification, and not the formation of GMV; especially in view of the need for a selective process to produce the mono-ester.

Further, the Examiner reasons that because **Beauchamp et al.** shows the recrystallization of acyclovir L-valinate hydrochloride (Method A), it would be obvious to crystallize GMVH. Appellants respectfully disagree. There is nothing in **Beauchamp et al.** (either alone or in combination with **Verheyden et al.**, which mentions only ganciclovir and not any ganciclovir esters) that would suggest that the finding of crystallinity for acyclovir L-valinate hydrochloride, where the only hydroxy group in the compound is esterified, should be capable of extrapolation to GMVH, where the compound contains both an esterified and an unesterified hydroxy group. Furthermore, as shown above, Appellants have shown that ganciclovir bis(L-valinate) hydrochloride is non-crystalline, so that it cannot be said to be obvious that GMVH would be capable of being prepared in crystalline form.

Accordingly, Appellants submit that **Verheyden et al.** in view of **Beauchamp et al.** does not suggest crystalline GMVH, and the rejection of Claims 23-28 as amended [to crystalline GMVH, to antiviral pharmaceutical compositions containing it, and to methods for its use in the treatment of infections with herpes simplex virus and cytomegalovirus, i.e. every claim requiring crystalline GMVH] under 35 USC 103(a) over **Verheyden et al.** in view of **Beauchamp et al.** should be withdrawn.

Withdrawal of the rejection is requested.

The Bioavailability Data

The Examiner has criticized the differences between the bioavailability data presented in the application, in the Memorandum of Record submitted with the Reply Brief mailed January 6, 1998 in the parent Application No. 08/453,223, and in the Declaration of Susan Malcolm submitted with the response mailed November 4, 1998, in the present application.

Applicants believe that the Malcolm declaration speaks for itself in giving the best data known to Applicants regarding the bioavailability of the compounds there discussed, based on a painstaking side-by-side comparison of the compounds. The difference between the results in the Malcolm declaration and in the application is explained as best it can by the Malcolm declaration: no further explanation is believed possible or necessary.

With regard to the data presented in the Memorandum of Record, Applicants' attorney states that such data were taken from the preliminary analysis of the experiments whose final analysis was presented in the Malcolm declaration, and this Memorandum of Record was prepared by him. With regard to the slight differences in the bioavailability values, these are understood to be due to recalculations based on purity analyses of the materials tested between the preliminary and final data reporting, and (as may be seen) are within the standard deviations expressed in the Malcolm declaration. With regard to the standard deviations, Applicants' attorney believes that he inadvertently reported the percentage standard deviations as percentages of the bioavailability value, rather than correctly, and as in the Malcolm declaration, as an absolute number around the bioavailability value. Thus, for example, the bioavailability of ganciclovir as reported in the Memorandum of Record is 6.9% ± (11.0% x 6.9)%, or 6.9% ± 0.76%, which is entirely consistent with the Malcolm declaration. A similar recalculation of the remaining "standard deviations" from the Memorandum of Record shows that they are consistent with, albeit not always identical to, the standard deviations given in the Malcolm declaration, with the differences believed to be due to the recalculations in the final data. Applicants' attorney regrets the error and the apparent lack of consistency in the results; however, he believed at the time of filing the Reply Brief in the parent application that it was important to ensure that the Office should know that the data reported in the application were no longer believed to be correct, and to advise the Office of the then-current data.

Further, while the data in the Malcolm declaration do show that valacyclovir hydrochloride has 53.4% bioavailability and valganciclovir hydrochloride has 55.4%, to consider this alone ignores the relative bioavailability of unesterified acyclovir and ganciclovir and the truly surprising increase in

bioavailability for ganciclovir when it is mono-esterified. Since the bioavailability of acyclovir is 14.2%, formation of the L-valinate ester increases the bioavailability approximately 3.8-fold. However, since the bioavailability of ganciclovir is only 6.9%, formation of the bis(L-valinate) ester increases the bioavailibility 4.9-fold, and formation of the mono(L-valinate) ester increases the bioavilability a further 1.6-fold, for an 8.8-fold increase over ganciclovir itself. It is thus truly surprising that formation of the mono(L-valinate) ester of ganciclovir would result in such a large increase in bioavailability.

The Provisional Double Patenting Rejection

Claims 23-28 were provisionally rejected for obviousness-type double patenting over Claims 51-56 of Application No. 08/453,223.

Application No. 08/453,223 has been expressly abandoned by a letter filed the same day as this response, and this rejection is therefore believed moot.

Conclusion

In view of the amendment and the declarations, and for the reasons given above, Applicants respectfully request that the rejections be reconsidered and withdrawn, and that amended Claims 23-28 be allowed.

Respectfully submitted,

Derek P. Freyberg
Attorney for Applicants
Reg. No. 29,250

Heller Ehrman White & McAuliffe
525 University Avenue
Palo Alto, CA 94301-1900
(650) 324-7014
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